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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,387	03/26/2001	Eckart Matthes	101195-24	9650

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	09/817,387	MATTHES ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-12 and 14-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-12 and 14-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. 1, 2, 5-12 and 14-22 are presently pending in the instant application.

3. Applicants elected (4/01/2003) the chimeric oligonucleotide described by SEQ ID NO: 16. It remains that sequences of SEQ ID NO: 1-15, and 17-28 are presently recited in instant claims 6, 8, and 16, however these sequences have not been searched since they are drawn to a non-elected invention.

New Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 2, 5-12 and 14-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, and those claims dependent therefrom, was amended to recite structures comprising a "P" moiety in the phosphorous linkage and outside the repeating units in each formula. Applicants must amend the formulas to use another term other than "P" to define the repeating unit since the term "P" is also used to define a phosphorous atom. Claim 1 goes on to define the term "p" in the claim, however the lower case "p" is not found in any of the structures.

Claim 9 recites "the oligonucleotides of claim 1, bound to telomerase.." There is lack of antecedent basis for this limitation in claim 9 since the scope of claim 1 is limited to chimeric oligonucleotides, however there is no support in claim 1 for wherein the oligonucleotide further comprises a bound telomerase or wherein the bound telomerase is in a cell as recited in claims 10-11 and 17.

Claims 14-15 recite "the method of claim 13," there is insufficient antecedent basis for this limitation in the claim, since claim 13 was cancelled by Applicants.

Claim 21 recite "the oligonucleotide of claim complexed with a cationic liposome," this phrase is vague and indefinite since it is unclear which claim Applicant's are referring to.

Response to Amendment

6. Applicant's amendment filed 10-23-06 complies with the requirements of 37 CFR 1.121(c)(2).

7. Claims 8, and 12, 14-15 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using chimeric oligonucleotides according to the present invention to inhibit telomerase activity *in vitro* comprising the administration of chimeric oligonucleotides, and provides guidance for inhibiting telomerase activity in human cancer cells transplanted into a nude mouse, does not reasonably provide enablement for using chimeric oligonucleotides of undefined structure and/or target, *in vivo* for treating cancer in all non-human mammals. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

8. Applicant's arguments filed 7-24-06 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that the examiner agrees that the Exhibit demonstrates enablement of the scope of the claimed invention that encompasses the inhibition of telomerase activity in human cancer cells transplanted into the flank region of a nude mouse, comprising the specific administration of. However, contrary to Applicant's assertions the instant claims are not limited to such a method. The instant claims clearly encompass administration of chimeric oligonucleotide to any mammal, including a human. As stated in the prior Office Action, in regards to the Exhibit submitted by Applicants in the reply filed 7-29-05, an opinion declaration is inefficient to establish actual evidence of full enablement of the claimed invention as of the filing date of the instant invention. Moreover, Applicant's argued that the Declaration provided as Exhibit 2 provides a summary of an experiment that shows using the chimeric oligonucleotides according to the present invention to inhibit telomerase activity in human cancer cells transplanted into a nude mouse. The examiner agrees that the Exhibit demonstrates enablement of the scope of the claimed invention that encompasses the inhibition of telomerase activity in human cancer cells transplanted into the flank region of a nude mouse.

Moreover, Applicants have not provided a correlation between their *in vitro* data and the production of *in viv*

5'-d(ACTGCTCAGA-GTTAGGGTTAG) 10mer/PS/T11/PAM
5'-d(ACTGCTCAGA-GTTAGGGTTAG) 10mer/PS/T11/Ome

l known in the art, as taught by Chirila et al. (2002), Jen (that at the time of the instant

invention, there is significant level of unpredictability associated with the behavior of antisense based oligonucleotides *in vivo*. Contrary to Applicant's assertions, in the unpredictable field of antisense therapy, the disclosure of the ability of one particular sequence to function successfully to inhibit telomerase, specifically, SEQ ID NO: 28 and 23, is not sufficient to provide evidence of the ability of other compounds comprising a distinct sequence and modification to inhibit the expression of telomerase in a tumor cell in vivo, comprising a non-specific route of antisense administration.

Additionally, it is noted that the scope of the present invention now reads on any mammal, human and non-human mammal. Applicants have not provided sufficient guidance and/or instruction that would allow the skilled artisan to use the oligonucleotide compounds according to the present invention in a method for the treatment of conditions associated with telomerase activity, for example cancer, in any non-human animal, other than in transplanted human cells in a nude mouse.

As stated in the prior Office Action, Chirila et al. (2002), Jen et al. (2000), and Stein (2000) teach that the behavior of oligonucleotide based compositions and their delivery *in vivo* are unpredictable, therefore claims to pharmaceutical compositions and methods of treating diseases by the administration of oligonucleotide based pharmaceuticals are subject to the question of enablement due to the high level of unpredictability associated with this technique as taught in the prior art. It was also previously stated that the quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that an undefined target nucleic acid is inhibited and the desired secondary effect of treating

tumors is obtained. The specification as filed provides no specific guidelines in this regard; the specification merely provides a prophetic example for using the claimed compositions *in vivo*.

Furthermore, the evidence provided in Exhibit 2 was specifically limited to tumor cells that were subcutaneously injected to into the flank area of a nude mouse, and wherein administration of the oligonucleotide was via an intraperitoneal route. The instant claims are not limited to the treatment of subcutaneous tumors via an intraperitoneal route. The results provided in the Declaration do not provide any evidence of the reduction of any particular therapeutic effect. There is no evidence that there was any correlation between the observed inhibition of telomerase expression and a corresponding reduction in tumor size.

This conclusion is based upon the known unpredictability regarding the behavior of oligonucleotide compositions in a cell, delivery of antisense *in vivo,* irrelevant cleavage of non-specific targets, the quantity of experimentation required to practice the full scope of the claimed invention (which reads on the therapeutic use of the claimed pharmaceutical composition) and the lack of guidance thereof in the specification as filed in this regard.

9. The rejection of claims 1-2, 5, 9-11 and 17 under 35 U.S.C. 102(b) as being anticipated by Uhlmann et al. for the reasons of record set forth Office Action mailed 11-17-03, is withdrawn in response to Applicant's amendment.

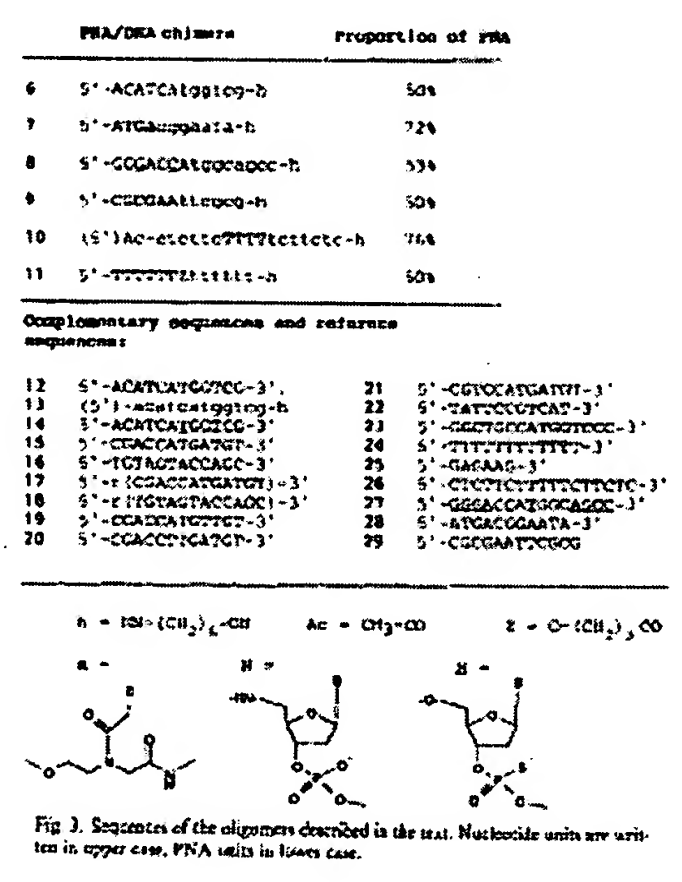
Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U. Uhlmann et al.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-2, 5, 7, 9-11, 17-20, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann et al. in view of Norton et al. (1996) and Mata et al.

12. Uhlmann et al. teach the synthesis and properties of PNA and DNA chimeras of any desired sequence by an automated synthesizer. In one particular embodiment, Uhlmann et al. disclose compounds of the following structure:



	PNA/DNA chimera	Proportion of PNA
6	5'-ACATCAtggtcg-h	50%
7	5'-ATGAcggaata-h	72%
8	5'-GCGACCAtgcrcgccc-h	53%
9	5'-CGCGAAttcgcg-h	50%
10	(5')Ac-ctcttcTTTTtcttctc-h	76%
11	5'-TTTTTTttttt-h	50%

Complementary sequences and reference sequences:

12	5'-ACATCATGGTCG-3',	21	5'-CGTCCATGATGT-3'
13	(5')-mcatcatggtcg-h	22	5'-TATCCCCTCAT-3'
14	5'-ACATCATGGTCG-3'	23	5'-GGCTGCCATGGTCCC-3'
15	5'-CGACCATGATGT-3'	24	5'-TTTTTTTTTTTT-3'
16	5'-TGTAGTACCAGC-3'	25	5'-GAGAAG-3'
17	5'-z(CGACCATGATGT)-3'	26	5'-CTCTTCTTTTTCTTCTC-3'
18	5'-z(TGTAGTACCAGC)-3'	27	5'-GGGACCATGGCAGCC-3'
19	5'-CCATCATGTTGT-3'	28	5'-ATGACGGAATA-3'
20	5'-CGACCTTGATGT-3'	29	5'-CGCGAATTCGCG

h = HN-$(CH_2)_6$-OH Ac = CH_3-CO z = O-$(CH_2)_3$-CO

Fig 3. Sequences of the oligomers described in the text. Nucleotide units are written in upper case, PNA units in lower case.

In compound **8** above we see underlined nucleotides, these correspond to nucleotides having a phosphorothioate linkages in the 5' portion of the molecule, and having PNA

oligomers on the 3' end of the structure. The oligonucleotide also comprises a 3' terminal amino group comprising an acid labile protecting group. However, Uhlmann et al. does not teach wherein **n** is at least 10 and not more than 20, and **p** is at least 3 and not more than 17. Moreover, Uhlmann et al. does not teach wherein this structure inhibits the activity of telomerase, or wherein the chimeric oligonucleotide structure comprises a terminal amino group.

Norton et al. teach the inhibition of human telomerase activity by peptide nucleic acids (PNAs). According to Norton et al. PNAs recognize the RNA component of human telomerase (hTR) and inhibit activity of the enzyme. Inhibition depends on targeting exact functional boundaries of the hTR template. Norton et al. also observed that phosphorothioate (PS) oligomers inhibit telomerase in a non-sequence selective fashion. Additionally, Mata et al. teach that hexameric phosphorothioate oligomers function to inhibit telomerase activity and arrests growth of Burkitts lymphoma cells.

It would have been obvious to the ordinary skilled artisan to combine the teachings of the above-cited references in the design of the present invention. Absent evidence of any unexpected results, one of ordinary skill in the art would have been motivated to make the oligomers of the present invention to comprise wherein **n** is at least 10 and not more than 20, and **p** is at least 3 and not more than 17, since the Uhlmann et al. clear teach that chimeric PNA/DNA oligonucleotides or any sequence can be readily prepared, and Norton et al. discloses the nucleotide structure of an oligomer (15 base pairs in length; i.e. satisfying **n** and **p**) that recognizes the RNA component of human telomerase and inhibits the activity of the enzyme. Furthermore,

in regards to the presence of a terminal primary amino group in the PNA oligomeric chimeras, it is noted that the compounds of Uhlmann et al. disclose a secondary amino group at the end of their chimeras, it is noted that the terminal secondary amino group in the compounds of Uhlmann et al. comprises an acid labile protecting group, which can readily be converted to a primary amino group via cleavage of the protecting group after synthesis is complete.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Janet L. Epps-Ford, Ph.D.
Primary Examiner
Art Unit 1633

JLE